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Long-term Effect of Vasodilator Therapy in Pulmonary Hypertension due to COPD: A Retrospective Analysis

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Abstract
Purpose Pulmonary hypertension (PH) due to COPD has dismal prognosis. We reviewed the long-term effect of PH-target therapy in severe PH-COPD.
Method Patients attending our PH-clinic were reviewed for PH-COPD receiving PH-target therapy. Baseline characteristics, death/transplantation until 2014, therapy, NYHA functional class, 6 min walk distance (6MWD) and oxygen saturation (SpO_2) at baseline, 3, 6, 12 and 24 months were analysed.
Results Of 48 PH-COPD identified 21 were excluded (insufficient data, comorbidity). 27 patients (7 females, 21 smokers, 23 emphysema) with median (quartiles) baseline age 70 (60; 76) years, FEV1 60 (46; 78) %, FEV1/FVC 57 (51; 64) %, DLCO 42 (36; 59) %, mean pulmonary artery pressure 39 (32;44) mmHg under inhaled iloprost (10), subcutaneous prostanoids (2), intravenous prostanoids (3), endothelin receptor antagonists (15) and phosphodiesterase-5-inhibitors (25) were included. Under therapy, NYHA functional class improved from 3.5 (3; 4) to 3 (2; 4) after 3 months and 3 (2; 3.5) after 6 months ($p = .02$ and .008). The 6MWD improved from 373 (236; 452) to 395 (339; 472), 414 (285; 492) and 396 (308; 497)m at 3, 6 and 12 months ($p = .005$, .006 and .011) with unchanged resting-SpO_2 but decreased peak-exercise SpO_2. During median follow-up of 5.9 (2.3; 8.4) years, 10 died, 2 were transplanted and 2 were lost to follow-up. Transplant-free survival at 1,2,3 years was 92,69,54 % and was similar for GOLD stages 1–4, but worse for patients with mPAP $\geq$40 mmHg ($p = .026$), 6MWD <370 m ($p = 0.008$), resting SpO_2 <92 % ($p = 0.02$) and peak-walk SpO_2 <87 % ($p = 0.012$).
Conclusion PH-target vasodilator therapy improved NYHA functional class and 6MWD up to one year in highly selected patients with severe PH-COPD. Poor exercise capacity, low SpO_2 and high mean pulmonary artery pressure at baseline but not airflow obstruction were associated with unfavourable outcome.

Keywords Pulmonary hypertension · Chronic obstructive pulmonary disease · Vasodilator therapy

List of Abbreviations

COPD	Chronic obstructive pulmonary disease
DLCO	Diffusion capacity of the lung for carbon monoxide
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
mPAP	Mean pulmonary artery pressure
NYHA	New York Heart Association
PH	Pulmonary hypertension

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PH-COPD	Pulmonary hypertension due to COPD
PAWP	Pulmonary artery wedge pressure
PVR	Pulmonary vascular resistance
QoL	Quality of life
RHC	Right heart catheter
6MWD	6 min walk distance
SpO_2	Peripheral oxygen saturation
WHO	World Health Organisation

Introduction

Pulmonary hypertension (PH) is defined by the World Health Organisation (WHO) as a mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest during right heart catheterization (RHC) and is classified into 5 major groups [1, 2]. After PH due to left heart diseases, PH due to chronic lung diseases is most common and within this, chronic obstructive pulmonary disease (COPD) is the most frequent cause owing to the high prevalence of COPD worldwide [3]. COPD is defined as a slowly progressive systemic disease, characterized by a fixed airflow obstruction by spirometry [4]. COPD has been classified by the global initiative for chronic obstructive lung disease (GOLD) in 4 categories according to the forced expiratory volume in 1 s (FEV1) [5]. According to the WHO, 210 million people are affected by COPD worldwide and it was estimated that around 3 million people died of COPD, which corresponds to 5 % of all deaths globally [3, 5]. Thus, COPD is a leading cause of morbidity worldwide and will become the fourth cause of mortality in 2030 [3]. The main cause of COPD is certainly cigarette smoking, especially in the western world, but also indoor and outdoor air pollution, occupational dusts and alpha-1-antitrypsin deficiency are important risk factors [3, 4].

Mild and typically exercise-induced PH is frequently found in COPD with increasing prevalence with more severe airflow limitation and PH in COPD is especially associated with chronic hypoxemia [6–8]. The prevalence of PH due to COPD (PH-COPD) is not well known, mainly as RHC is not done routinely and the prevalence may vastly vary according to the setting (ambulatory, general practitioners vs. specialist centres with severe cases). Despite PH-COPD usually being mild (mPAP <30 mmHg), some patients develop a severe and rapidly progressive PH (mPAP ≥35 mmHg) leading to death or necessitating lung transplantation [8–10]. The latter are sometimes called "out of proportion" cases, although this terminology has never been standardized and is abandoned by some experts [9]. It is important to know, that the severity of airflow obstruction does not correlate with the mPAP and thus, PH might be observed with mild airflow limitation [7, 9]. PH in COPD is a significant risk factor for hospitalization, for acute exacerbation and is associated with a worse survival [11, 12]. Main pathogenetic mechanisms involved in PH-COPD are hypoxic pulmonary vasoconstriction, remodelling of pulmonary vessels, inflammation, pulmonary microthrombosis and the reduction in the number of pulmonary vessel in emphysema [6, 13].

Up to now, there is no specific therapy for PH-COPD [9]. According to pathogenesis, smoking cessation, long-term oxygen therapy and treatment of airflow obstruction by inhalation therapy or treatment of right heart failure by diuretics are therapeutic cornerstones [9]. Treatment with vasodilator therapy as used for pulmonary arterial hypertension, namely prostanoids, endothelin receptor antagonists (ERA) and phosphodiesterase-5-inhibitors (PDE5I), is not recommended due to the lack of randomized controlled trials and the fear that they may impair gas exchange due to pulmonary vasodilation and increased ventilation–perfusion mismatch [9, 14]. On the other hand, favourable antiproliferative and vasodilator effects of PH-target therapy (prostanoids, ERA and PDE5I) might be of value in some patients with severe PH-COPD in order to reduce the afterload of the right heart, in analogy to other forms of PH [9, 15]. In lack of RCT, the aims of the present study were to identify all patients with PH-COPD who received PH-targeted therapy for at least 3 months, to look at changes in exercise performance, quality of life (QoL), functional class, hemodynamic, blood oxygenation, safety and event-free survival with these therapies.

Methods

Patients

Datasets of all patients attending our PH-outpatient clinic were reviewed, in this retrospective data analysis, to identify patients with PH-COPD. Patients were included if they had PH defined as mPAP ≥25 mmHg with a pulmonary artery wedge pressure (PAWP) ≤15 mmHg during right heart catheterisation along with a diagnosis of COPD defined as FEV_1/FVC <0.7 and if PH-target therapy had been started and taken for at least 3 months. PH-target therapy was defined as parenteral prostanoids, ERA and PDE5I. Patients were excluded if they had another reason for their PH, namely chronic left heart disease (PAWP ≥15 mmHg), thromboembolic PH, PH associated with connective tissue diseases, interstitial or other significant parenchymal lung disease at high resolution thoracic CT, other PH classification (HIV, drugs- and toxins) or a combination of these. The outpatient clinic database was searched to identify cases diagnosed with PH from January 2000 to end of December 2013. The study was approved by

the Cantonal ethical review board Zurich (KEK-2013-0553).

Data Retrieval, Analysis and Statistics

All patients' records were thoroughly reviewed and the following characteristics and parameters noted at baseline just before the start of PH-target therapy: age, sex, smoking status and history, pulmonary function test, the presence of emphysema at chest computed tomography, pulmonary hemodynamics by right heart catheterisation and echocardiography, haemoglobin, NT-pro-brain natriuretic peptide (NT-pro-BNP), 6MWD, New York Heart Association (NYHA) functional class and QoL (Minnesota living with heart failure questionnaire;MLHF).

According to the practice at our PH-clinic, patients under PH-target therapies have regular follow-up visits at 3, 6, 12 and 24 months and at least yearly thereafter with assessments of 6MWD, NYHA class, MLHF and NT-pro-BNP. This close follow-up allowed having complete follow-up (defined as death or lung transplantation).

Descriptive statistics for median (quartiles) were used, and analysis of variance for repeated measures (Friedman-test) and Wilcoxon matched pair tests were used to compare baseline values with values after 3, 6, 12 and 24 months of therapy. Event-free survival was calculated by Kaplan-Meier analysis over all PH-COPD patients and stratified by disease severity, namely by GOLD-classes, the medians of mPAP or SpO_2 at rest and peak-walk. Cox regression was used to look for the predictive value of baseline valuables or changes with therapy after 3 months. Pearson's correlation between PH and COPD was calculated. A $p < 0.05$ was considered significant.

Results

From 493 PH-datasets, 48 were classified as PH-COPD. 21 had to be excluded due to diagnostic failure, comorbidity or no PH-target therapy (Fig. 1). Characteristics of 27 included patients are shown in Table 1. 3/4 of patients were male smokers (1/5 persistent) and severely limited (half in NYHA class IV) with a markedly reduced 6MWD. Airflow limitation was comparably mild with a median FEV_1 of 60 % and the majority being in Gold stage I or II, emphysema was documented in 92 %. Pulmonary hemodynamics were severely compromised [mPAP of 39 (32; 44) mmHg]. Most patients had single bronchodilator therapy; inhaled steroids were used in half. 60 % of patients used supplemental oxygen at least during nights, 89 % were anticoagulated. The NT-pro-BNP was elevated [653 (159; 1,194) ng/l, normally <300 ng/l]. We found no correlation between COPD severity according to baseline FEV_1 and the baseline mPAP or PVR, but both parameters significantly correlated with the baseline SpO_2.

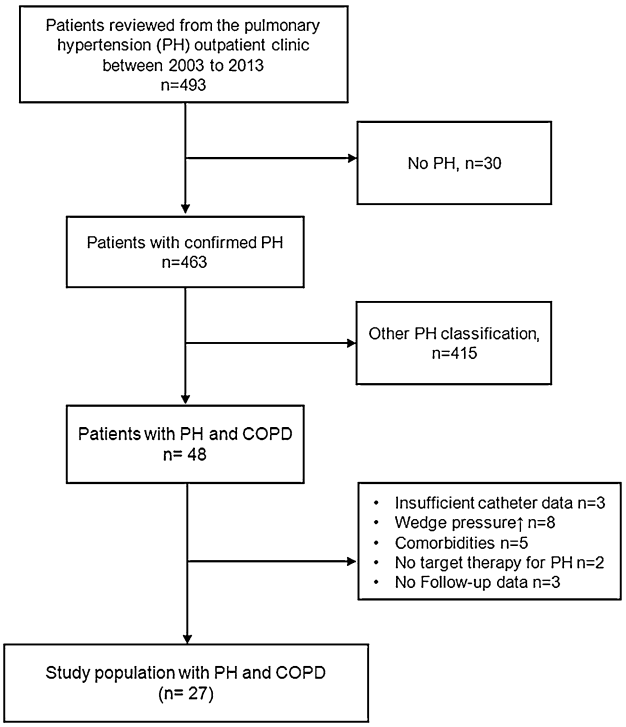

Fig. 1 Patient flow. *COPD* chronic obstructive pulmonary disease, wedge pressure pulmonary artery occlusion pressure. Target therapy: parenteral prostanoids, endothelin receptor antagonists (ERA) and phosphodiesterase-5 inhibitors (PDE5I)

Patients' PH-target-therapy initiated at baseline and their maximal therapy during the observational period is shown in Table 2. Most patients were treated with PDE5I, followed by ERA and inhaled prostanoids.

Table 3 shows the course of markers of disease severity under therapy: the NYHA improved significantly from 3.5 (3; 4) at baseline to 3 (2; 4) at 3 months and 3 (2; 3.5) at 6 months ($p = .020$ and .008). After 1 and after 2 years instead, the values returned to baseline. Figure 2 visualizes changes in NYHA. The 6MWD test increased significantly from 373 m (236; 452) at baseline to 395 m (339; 472) after three months to 414 m (285; 492) after 6 months and to 396 m (308; 497) at 12 months ($p = .005$, .006, .011). After 2 years, the median was insignificantly higher compared to baseline 434 (277; 508). Changes of the 6MWD are shown in Fig. 3.

The SpO_2 did not change under therapy, whereas the peak-exercise SpO_2 decreased to 83 (76; 88, $p = .014$) after 3 months, 81 (76; 87, $p = .014$) after 6 months, 82 (80; 88.5, $p = .116$) after 1 year and 83.5 (73; 89.5, $p = .039$) after 2 years (Fig. 4). Heart rate, QoL, NT-pro-BNP and tricuspid pressure gradient did not change.

Table 1 Baseline characteristics of patients with chronic obstructive pulmonary disease and pulmonary hypertension

	Number (%) median (IQR1; IQR3)
Total number of patients	27 (100)
Females	7 (26)
Age (years)	70 (60; 76)
BMI (kg/m^2)	26 (24; 30)
Current smokers	5/26 (19)
Past smokers	21/26 (81)
Peak years smoked until baseline	40 (5; 50)
Peak years total	40 (5; 50)
NYHA functional class II/III/IV	3/9/12 (12.5/37.5/50)
6 min walk distance (m)	373 (236; 452)
Resting peripheral oxygen saturation (%)	92 (86; 94)
Peak exercise peripheral oxygen saturation (%)	87 (79; 91)
Resting heart rate (min^{-1})	83 (76; 93)
Peak exercise heart rate (min^{-1})	112 (101; 123)
COPD severity by GOLD stage I/II/III/IV	6/12/6/3 (22/44.5/22/11.5)
Pulmonary function tests (% predicted)	
Forced expiratory volume in 1 s (FEV_1 % predicted)	60 (46; 78)
Forced vital capacity (FVC % predicted)	84 (63; 105)
FEV_1/FVC	57 (50.5; 64)
Total lung capacity (% predicted)	103 (90; 116)
Residual volume (% predicted)	127 (105; 189)
Carbon monoxide diffusion capacity (% predicted)	42 (36; 59)
Emphysema at thoracic computed tomography	23/25 (92)
Pulmonary hemodynamics	
Mean pulmonary artery pressure (mmHg)	39 (32; 44)
Cardiac index [(l/min m^2)]	2.4 (2.2; 3.1)
Pulmonary vascular resistance (dyn s/m^5)	420 (357; 529)
Right atrial pressure (mmHg)	7 (5; 9)
Pulmonary artery occlusion pressure (mmHg)	11 (9; 12)
Tricuspid pressure gradient by echocardiography (mmHg)	57.5 (45.75; 69.25)
Haemoglobin (g/l)	15 (14; 16)
NT-pro-BNP (ng/l)	653 (159; 1,194)
COPD target therapies	
Inhaled bronchodilators (long acting beta agonist)	17/27 (63)
Inhaled bronchodilators (long acting muscarinic antagonist)	11/25 (44)
Inhaled corticosteroids	15/27 (56)
Oral anticoagulation	24/27 (89)
Supplemental oxygen	16/27 (60)

BMI body mass index, *NYHA* new york heart association, *COPD* chronic obstructive pulmonary disease, *GOLD* global initiative for chronic obstructive pulmonary disease, *NT-pro-BNp N*-terminal pro b-type natriuretic peptide

Table 2 Pulmonary hypertension- target therapies started at baseline and maximal therapy

	Number (%)
PH-target therapies started at baseline	
Prostanoid inhaled	5/27 (18.5)
ERA (endothelin receptor antagonist)	8/27 (30)
PDE5I (phosphodiesterase type 5 inhibitor)	14/27 (52)
Maximal PH-target therapies over whole period	
Prostanoid inhaled	10/27 (37)
Prostanoid subcutaneous	2/27 (7.5)
Prostanoid intravenous	3/27 (11.5)
ERA (endothelin receptor antagonist)	15/27 (55.5)
PDE5I (phosphodiesterase type 5 inhibitor)	25/27 (93)

Two patients stopped therapy with ERA. 1 pre-treated with sildenafil after 1 month in lack of efficacy and worsening leg oedema, 1 was switched to PDE-5 inhibitor after 3 months in lack of efficacy. The later was thereafter well supported until now (4 years). Three patients stopped therapy with PDI-5 inhibitors after a mean time of 1.6 (1–3) months due to lacking efficacy. All had been pre-treated (2 with ERA, 1 with inhaled iloprost).

We found a positive correlation between the mPAP and PVR at baseline and the change in the 6MWD after 3 months ($p = .01$, $R = .514$ and $p = .005$, $R = .563$). The changes in 6MWD over time did not correlate with other baseline parameters.

During the median follow-up of 5.9 (2.3; 8.4) years, 10 patients died [after 3.1 (2.3; 4.3) years], 2 patients were transplanted [after 2.7 (1.7; 3.6) years], and two were lost to follow-up [after 3.3 (2.2; 4.4) years]. Kaplan–Meier survival analysis shows that patients with an mPAP $\geq$40 mmHg (14 patients) had worse transplant-free survival compared to patients with lower mPAP ($p = .026$, Fig. 5). The transplant-free survival of patients with a baseline 6MWD <370 m (14 patients) was significantly worse compared to patients with better 6MWD ($p = .026$, Fig. 6). Additionally, patients with a resting SpO_2 <92 % ($p = .02$, 13 patients) and with a peak-exercise SpO_2

Table 3 Course of characteristics under therapy

Characteristics	3 months	*n*	*p* value	6 months	*n*	*p* value	12 months	*n*	*p* value	24 months	*n*	*p* value
nnnNYHA functional class	3 (2; 4)	23	0.020	3 (2; 3.5)	17	0.008	3 (4; 2)	21	0.429	3 (2; 4)	15	0.655
6 min walk distance (m)	395 (338.5; 472)	25	0.005	414 (285; 492)	19	0.006	396 (308; 497)	23	0.011	434 (277; 508)	16	0.163
Borg scale	4 (4; 5)	23	0.303	4 (4; 5)	17	0.315	4.5 (4; 6.25)	22	0.736	5 (4; 6)	16	0.971
Resting peripheral oxygen saturation (%)	90 (84; 95)	22	0.286	90 (87.5; 94)	17	0.775	91 (86.5; 94)	21	0.358	89 (86; 91)	15	0.156
Peak exercise peripheral oxygen saturation (%)	83 (75.5; 88)	22	0.014	81 (76; 87)	17	0.014	82 (80; 88.5)	21	0.116	83.5 (73; 89.5)	16	0.039
Resting heart rate (min^{-1})	85 (80.5; 92.5)	21	0.408	84 (74.5; 104)	16	0.979	84 (77; 94)	21	0.689	84 (72.5; 95)	16	0.272
Peak exercise heart rate (min^{-1})	120 (106; 136)	21	0.053	120 (105; 131.5)	17	0.063	121 (102; 132.5)	21	0.104	116 (102; 134)	16	0.100
LHFQ total	37 (20; 59.5)	13	0.058	38 (28; 52)	11	*	36 (23.5; 48)	13	0.367	18.5 (6; 31)	8	*
LHFQ physical subscore	18 (11; 26)	13	0.440	20 (15; 24)	11	*	19 (14.5; 22)	13	0.504	10.5 (4.25; 17)	8	*
LHFQ emotional subscore	6 (3; 14)	13	0.156	5 (2; 13)	11	*	5 (2; 13)	13	0.502	1 (0; 4.5)	8	*
NT-pro-BNP (ng/l)	594 (167; 1,178)	18	0.078	525 (198; 1,340)	12	*	294 (148; 1,450)	19	0.938	769 (184; 1,951)	12	*
Tricuspid pressure gradient (mmHg)							45 (43.5; 60.50)	24	0.181	50.5 (39; 66)	8	*

Data given as median (quartiles)

NYHA new york heart association, *LHFQ* the minnesota living with heart failure questionnaire (higher values associated with worse quality of life), *NT-pro-BNp* *N*-terminal pro b-type natriuretic peptide

* Data available for less than 13 patients, hence the *p* values are not displayed

<87 % ($p = .012$, 11 patients) had worse transplant-free survival. Transplant-free survival was not different according to GOLD stages or therapies. Cox regression revealed that the 6MWD was the only predictor of transplant-free survival ($\beta = .006$, $p = .039$) whereas age, FEV1 ($\beta = .012$, $p = .51$), mPAP ($\beta = .078$, $p = .08$), PVR ($\beta = .003$, $p = .07$) and SpO_2 ($\beta = -.128$, $p = .126$) were not.

Discussion

In this retrospective study in highly selected patients with severe PH-COPD treated at a specialized PH-center, we found that pulmonary selective vasodilator PH-target therapy improved functional class and 6MWD, with sustained improvements over 1 year. Event-free survival was better with better hemodynamics, exercise performance and blood oxygenation, but was not influenced by airflow limitation.

One of the complications of COPD is that patients may develop PH. However, the epidemiology of PH-COPD is incompletely known and vastly varies according to the setting (ambulatory patients, regional hospitals, intensive care units, tertiary care centres with specialized units) [6, 9]. In advanced COPD before lung volume reduction surgery or transplantation, a PH prevalence of >50 % was found [10, 16]. The prevalence of PH-COPD differed by GOLD stages with 5, 27 and 53 % for stages II, III and IV [17]. PH in COPD is prognostically important; however, RCT for PH-therapy for these patients are lacking [6, 9, 12]. In the present retrospective analysis of PH-target therapy in a highly selected collective of patients, we found that functional class and the 6MWD improved for up to 2 years. The resting SpO_2 was unaffected by therapy whereas peak exercise SpO_2 decreased. These findings are in line with a RCT in 37 patients with PH-COPD, who were treated with sildenafil, which found an improved exercise performance and a reduction of mPAP in patients with severe PH-COPD under PDE5I-therapy [18]. However, other studies reached contradictive results. Lange et al. recently described a better survival in a retrospective cohort of treated PH-COPD, but no effect of therapy on the exercise capacity [19]. Blanco et al. investigated the effect of sildenafil given for 3 months in addition to training to COPD patients with mild PH at echocardiography [20]. The improvements under training were similar in the sildenafil- and placebo-treated groups with similar changes in oxygenation and quality of life [20]. Others have shown that the increase of mPAP during exercise was attenuated by sildenafil; however, the exercise capacity did not improve [21]. It is important to note that the latter study analysed data of 18 COPD patients among whom just 5 had

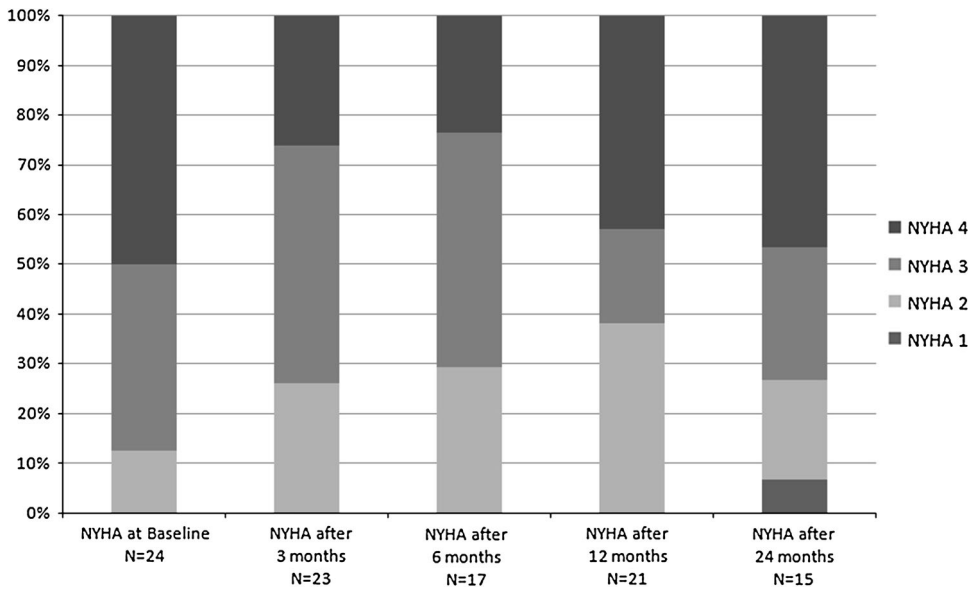

Fig. 2 New York Heart Association functional class (NYHA): course under therapy. Data given as percent. N = number of patients assessed

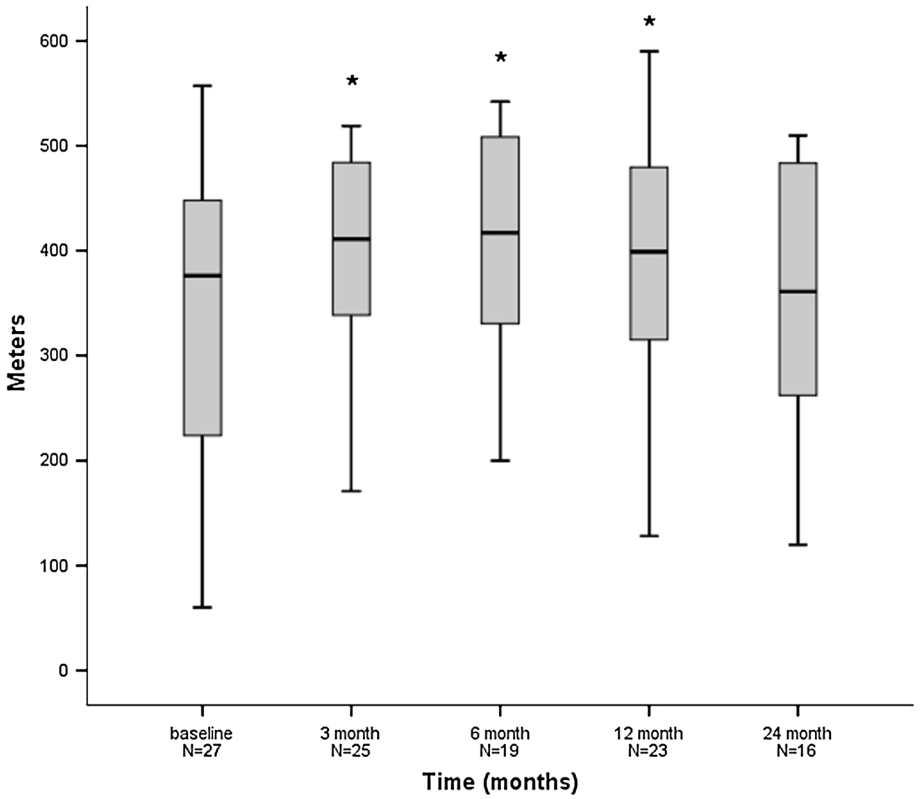

Fig. 3 Evolution of the 6 min walk distance in metres under therapy. Data given as median (quartiles). *$p < .05$. N = number of patients assessed

PH. Others showed that exercise capacity and stroke volume did not improve under sildenafil in a collective of COPD patients in whom not all had PH [22]. In another COPD-collective without resting PH, exercise capacity was not increased by sildenafil but the gas exchange and QoL were impaired under therapy along with more adverse events [23]. There are few studies analysing the effect of bosentan in patients with COPD, and the results seem to be controversial. One study showed a positive effect of bosentan in patients with PH-COPD [24], the therapy seemed to stop the progressive increase of mPAP and PVR. Another study found no improvement in exercise capacity, but deterioration of hypoxemia and functional status [25]. Of note, this study included patient with COPD without or only mild PH as assessed by echocardiography and not RHC [25]. Thus, the heterogeneity of response to PH-target

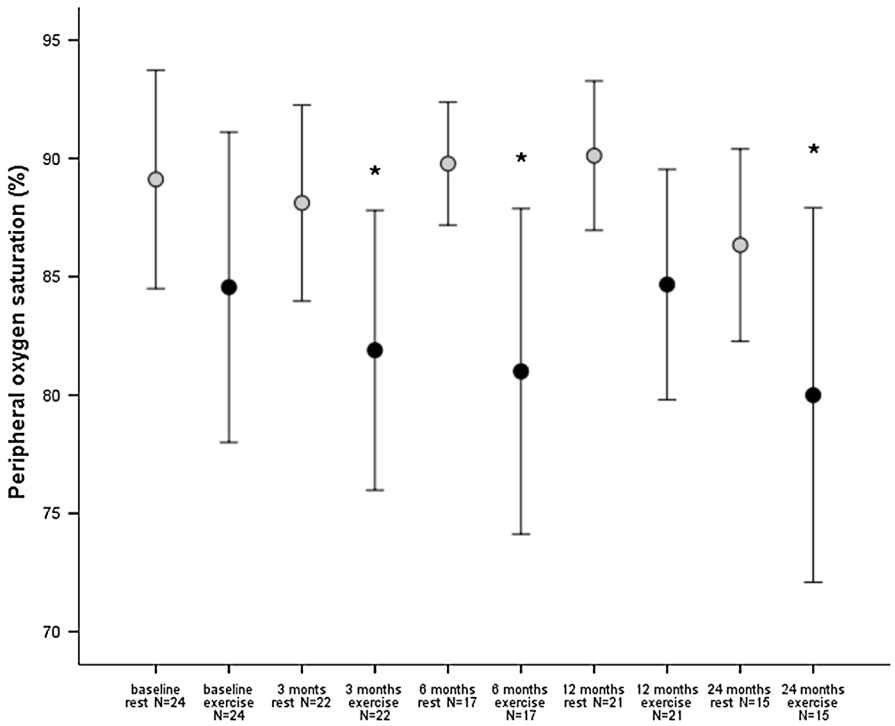

Fig. 4 Peripheral oxygen saturation: comparison between rest and peak exercise oxygen saturation at baseline and under therapy after 3, 6, 12, 24 months. 95 % confidence intervals, data given as median, N = number of patients assessed

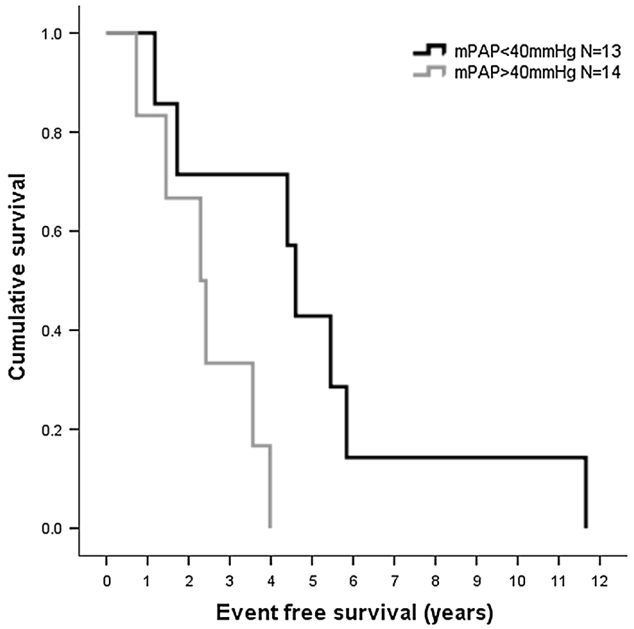

Fig. 5 Kaplan–Meier survival plots are shown for patients with mean pulmonary artery pressure of >40 and <40 mmHg. N = number of patients assessed

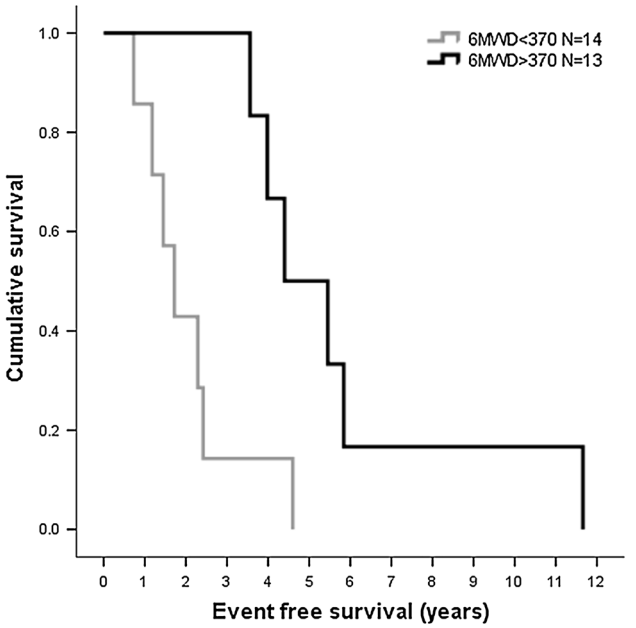

Fig. 6 Kaplan–Meier survival plots are shown for patients with a 6 min walk distance <370 and >370 m. N = number of patients assessed

therapy might be due to patients' selection and the presence of relevant PH.

We analysed the development of SpO_2 during therapy at rest and at peak exercise in the 6MWD test. We found that resting SpO_2 did not change under PH-target therapy, whereas peak exercise desaturation increased along with an increased exercise capacity. Thus, our results may support an increased ventilation–perfusion mismatch at peak exercise however along with an increased exercise capacity potentially due to a decreased RV afterload. A study investigating the acute effect of sildenafil during exercise in PH-COPD showed a reduced mPAP and PaO_2 at rest

under therapy; however, only the mPAP further decreased with exercise but not the PaO_2 [26]. In regard to prostanoids contradictory effects on ventilation–perfusion mismatch were reported. In a study investigating 26 patients with exacerbated COPD, prostaglandin E1 given intravenously (IV) decreases mPAP without worsening blood gases [27]. On the other hand, in a placebo-controlled trial in 16 COPD patients with acute respiratory failure, PVR reduction under IV-prostanoids was only temporary and accompanied by a significant fall in SpO_2 [28]. Similar unfavourable effects of IV-prostanoids were found by others [29, 30]. In our cohort, only 3 patients received IV-prostanoid as rescue therapy. The first of these 3 patients was transplanted after 4.6 year, the second died after 2.6 years and the third survives for 5 years now. Five patients in our cohort were treated with inhaled iloprost. Inhaled iloprost potentially acts preferentially in well-ventilated regions of the lung, thereby reducing PH with less effect ventilation–perfusion mismatch [31]. Others did not find an improvement of exercise capacity and showed that the oxygenation at rest deteriorated [32]. Since results of PH-target therapies in PH-COPD are so controversial, there is an obviously need for further and more in depth studies in collectives of COPD patients with relevant PH with exact characterization of hemodynamics by right heart catheterisation, gas exchange and airflow limitation.

In our study, we found a marginally insignificant improvement in QoL ($p = .058$) after 3 months of treatment. Unfortunately, in our retrospective analysis not all patients did have regular QoL assessments. However, this important patient-centered outcome should be assessed in future, well-performed trials.

PH-COPD is associated with worse survival [6, 11, 12]. This could be confirmed in our study, as patients with a mPAP >40 mmHg had a worse event-free survival. Similarly, patients with 6MWD <370 m and low resting or peak-exercise SpO_2, but not patients with worse GOLD stages had worse event-free survival. This may indicate that pulmonary hemodynamics and impaired blood oxygenation are prognostically more important than mere airflow limitation in this COPD-collective with marked PH and thus strengthen the need for effective therapies to improve PH without affecting gas exchange in this potentially vast collective. Of note, most of these patients had a relatively good GOLD stage, this might be the reason why we did not found a prognostic relevance of FEV1 in this collective.

The only parameter which predicted the patients' event-free survival in cox regression was the 6MWD at baseline, but not the change in 6MWD or other parameters. Other studies have emphasized the importance of exercise capacity as outcome parameter in COPD, e.g. Pinto-Plata et al. showed that the 6WMD in patient with severe COPD is a better predictor of mortality than the degree of obstruction, BMI and associated comorbidities [33, 34].

Our study has the following limitations: As this is a retrospective data analysis, not all patients had regular follow-up available at each time-point and thus, we do not know whether the results would have been different if all patients would have had every outcome. The retrospective design is also limited by potential selection and referral bias: Our PH-COPD cohort was retrieved from a specialist PH-outpatient clinic. This might explain why the mPAP was relatively high and thus the results are not transferable to COPD patients with mild or only exercise-induced PH. In addition, our study was too small to look at the different PH-target therapy classes separately. Accordingly, we are not able to draw inference on these aspects and it may well be that one therapy outreaches another. Despite these drawbacks, in lack of RCTs in the field, we believe that it is important to collect as much information as possible on the effect of PH-target therapy in selected PH-COPD collectives until data from well-designed RCTs get available.

Conclusions

In this selected cohort of patients with severe PH-COPD, PH-target vasodilator therapy did improve NYHA functional class and 6MWD without worsening resting SpO_2 for up to 1 year. Poor exercise capacity, SpO_2 and high mPAP at baseline were associated with shortened transplant-free survival but not worse airflow obstruction. The baseline 6MWD was the only independent predictor of survival.

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